Case report

Olfactory training with essential oils for patients with post-COVID-19 smell dysfunction: A case series

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ABSTRACT

Introduction: It is estimated that up to one third of COVID-19 patients can develop long-lasting smell dysfunction. Viral infections, especially COVID-19, can cause anosmia through different pathomechanisms, and different strategies have been proposed for effectively managing post-COVID-19 olfactory dysfunction in clinical practice, with olfactory training being recommended as a first-line treatment option.
Methods: This report describes a non-consecutive series of clinical cases. After COVID-19, eight cases (5 females, 3 males) of adult patients with long-lasting (3+ months) post-viral smell dysfunction followed a 30-day olfactory training protocol with a set of plant-derived essential oils. At baseline and at the end of the treatment, the patients were administered the Assessment of Self-reported Olfactory Functioning (ASOF) questionnaire, an inventory used to measure olfactory dysfunction and health-related quality of life.
Results: For any of the outcomes assessed with the ASOF scale, a significant improvement from baseline was reported, even though mean value ameliorations were more pronounced for olfactory function per se (Subjective Olfactory Capability: from 3.6 to 5.6 out of 10; Self-Reported capability of Perceiving specific odors: from 1.8 to 3.0 out of 5), rather than for health-related quality of life (Olfactory-Related Quality of life: from 2.9 to 3.9 out of 6).
Conclusions: It was observed that patients with long-lasting COVID-19-related smell dysfunction improved after a 30-day olfactory training protocol. Further controlled clinical studies would be useful to better investigate the role of olfactory training in patients with postviral smell dysfunction.

1. Introduction

It is estimated that up to one third of COVID-19 patients can develop long-lasting smell dysfunction, including parosmia (qualitative distortion of the normal sense of smell), hyposmia (reduced ability to detect odors) and anosmia (complete inability to detect odors) [1]. Viral infections, especially COVID-19, can cause anosmia through different pathomechanisms, including inflammation of the nasal epithelium, early apoptosis of olfactory cells, changes in odor transmission, alterations of nasal cilia, and damage of olfactory neurons and microglial cells [2].

Different strategies have been proposed for effectively managing post-COVID-19 olfactory dysfunction in clinical practice, with olfactory training being recommended as a first-line treatment option, along with a healthy diet, lifestyle changes (smoking cessation), and, in selected cases, corticosteroid drug therapy [3]. Since very limited treatment options exist for post-viral olfactory dysfunction and the prevalence of this health condition has markedly increased worldwide with the COVID-19 pandemic [1], this report aims to share our observations on a small sample of patients treated with a 30-day olfactory training protocol based on plant-derived essential oils already used in clinical aromatherapy.

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2. Methods

2.1. Information about the patients, clinical findings and timeline

The CARE guidelines were followed to report our study results [4]. Here we describe eight cases (5 females, 3 males) of nonsmoker adult patients (age range: 25–66 years, median: 52.5 years) with long-lasting (3+ months) smell dysfunction after COVID-19, who followed a 30-day olfactory training protocol with a set of plant-derived essential oils. The most important characteristics of the cases described in this report are summarized in Table 1. None of the patients had severe comorbidities or suffered from previous Ear-Nose-Throat disorders; some of them took medicinal drugs every day for chronic illnesses, mostly cardiovascular, metabolic, and endocrine diseases. All patients were diagnosed with COVID-19 (positive nose swab PCR test) when they first developed anosmia, and this symptom either persisted as was after the viral infection resolution or turned into hyposmia or parosmia over time (Table 1). COVID-19 symptoms reported by the patients were not severe, as none of them developed respiratory insufficiency or life-threatening complications during the acute phase of SARS-CoV-2 infection. On average, the amount of time between the symptoms onset and the first olfactory training session was 6.5 ± 3.2 months (mean±SD).

2.2. Informed consent and ethics clearance

The informed consent was provided by the patients on a free and voluntary basis, and clinical data were fully anonymized, as per national and European laws ("GDPR - Regolamento 2016/679"). This research was conducted in accordance with the Declaration of Helsinki and its subsequent modifications [5]. Ethics approval was waived because of specific regulations of the local ethics committee: in fact, both the administration of the intervention and the outcome assessment were part of the patients' routine care performed by two of the authors (D.D. and M.A., both licensed physicians). The COPE recommendations were followed and a blank copy of the patients' informed consent is available for consultation in the Appendix [6].

2.3. Diagnostic assessment and therapeutic intervention

After a baseline medical check-up (T0), the patients with post-COVID-19 smell disorders who sought medical advice were offered to follow an olfactory rehabilitation protocol: those who agreed, provided their written informed consent and were instructed to do the olfactory training at home.

When collecting the patients' medical history, it was assured that they were not allergic to any of the essential oils administered. The 30-day protocol included two olfactory training sessions every day (one in the morning and the other one in the evening), each of them lasting approximately 15 min. During every session, the patients had to smell a set of ten plant-derived essential oils through different patterns (deep inhalation, rapid sniffing) and in a pre-specified order, as follows:

1 Peppermint (*Mentha x piperita* L.) essential oil is dominated by (-)-menthol, which has a refreshing, cool and mint note, and binds to M8 [7], A1 [8] and V3 [9] TRP channels.

2 Lavender (hybrid) (*Lavandula x intermedia* Emeric ex Loisel) essential oil is dominated by R-(-)-linalool, which has a flowery-fresh odor, has been described as "herbaceous" in Roudnitska's classification [10], and binds to A1 [11] and M8 [12] TRP channels.

3 Lemon (*Citrus × limon* (L.) Osbeck) essential oil is dominated by (+)-limonene, which has a fresh, pleasant, orange-like smell, and has been described as member of the "fruity" category in Henning's classification [13], and a member of the "Citrus" category in Roudnitska's classification [10].

Table 1
A brief summary of the patients' clinical characteristics.

Case ID	Sex	Age	COVID-19 onset	OT protocol	COVID-19 symptoms Anosmia	Dysgeusia	Systemic	RI	ENT disorders	Comorbidities	Medicinal drugs	Olfactory symptoms Early olfactory dysfunction	Late olfactory dysfunction (3 months after infection)
1	F	52	Nov-20	May-21	Yes	Yes	Yes	No	No	Bronchiectasis, psoriasis, past SAH	OCP	Anosmia	Parosmia
2	F	25	Dec-20	May-21	Yes	Yes	Yes	No	No	No	OCP	Anosmia	Parosmia
3	M	66	Nov-20	Jun-21	Yes	Yes	No	No	No	No	No	Anosmia	Hyposmia
4	M	27	Feb-20	May-21	Yes	Yes	Yes	No	No	No	No	Anosmia	Parosmia, hyposmia
5	M	64	Jan-21	May-21	Yes	Yes	No	No	No	Hypertension, hypercholesterolemia	Statin, beta blocker	Anosmia	Anosmia
6	F	53	Dec-20	Jun-21	Yes	Yes	No	No	No	No	Levothyroxine	Anosmia	Parosmia, hyposmia
7	F	45	Feb-21	Jun-21	Yes	Yes	Yes	No	No	Hypothyroidism	Levothyroxine	Anosmia	Parosmia, hyposmia
8	F	63	Nov-20	May-21	Yes	Yes	Yes	No	No	Hypercholesterolemia, hypothyroidism	Statin, levothyroxine	Anosmia	Hyposmia

Table legends.
ENT=Ear-Nose-Throat.
OCP=Oral Contraceptive Pill.
OT protocol=Olfactory Training protocol (first session date).
RI=Respiratory Insufficiency.
SAH=Subarachnoid Hemorrhage.
*=Taste perception: Y=Yes; N=No; A=Altered.

4 Red spruce (*Picea abies* (L.) H. Karst) essential oil is dominated by camphene, alpha- and beta-pinenes, and has a typical pine-like odor.

5 Frankincense (*Boswellia sacra* Flueck) essential oil is dominated by (E)-β-ocimene and monocyclic monoterpene hydrocarbons, such as (+)-limonene. (+)-Limonene has a fresh, pleasant and orange-like smell.

6 Hyssop CT. pinocamphone (*Hyssopus officinalis* L.) essential oil is dominated by monoterpene bicyclic ketones, such as pinocamphone and iso-pinocamphone, and belongs to the "spice" and "herbaceous" categories in Roudnitska's classification [10].

7 Cinnamon (*Cinnamomum verum* J. Presl) essential oil is dominated by the aromatic aldehyde cinnamaldehyde, which binds to A1 [8] and V3 [14] TRP channels, and has a warm-spicy odor. This essential oil belongs to the "spice" category in Roudnitska's classification [10].

8 Cloves (*Syzygium aromaticum* (L.) Merr. & L.M.Perry) essential oil, characterized by a spicy odor, is dominated by the aromatic aldehyde eugenol, which binds to A1 [8], V3 [15] and M8 [16] TRP channels. This essential oil belongs to the "spice" category in Henning's [13] and Roudnitska's [10] classifications.

9 Savory (*Satureja montana* L.) essential oil is dominated by the terpenic phenol carvacrol, which binds to A1 [15], V1 [17], V3 [15] and M7 [18] TRP channels. This essential oil belongs to the "herbaceous" category in Roudnitska's classification [10].

10 Eucalyptus (*Eucalyptus globulus* Labill) essential oil is dominated by the monoterpenic oxide 1,8-cineole, which has a characteristic penetrating fresh smell and binds to M8 [19], A1 [19] and V3 [9] TRP channels. This essential oil belongs to the "resinous/ethereal" category in Henning's classification [13].

2.4. Follow-up and outcomes

In order to assess any clinical improvements, the patients were administered the ASOF questionnaire, a self-reported inventory used to measure olfactory dysfunction and health-related quality of life [20]. The questionnaire was filled out by the patients both at baseline (T0), and at the end of the treatment (T1), when intervention adherence and tolerability were assessed with a short interview. None of the patients reported any adverse effect or discontinued the treatment in advance for any reason.

The ASOF scales include the Subjective Olfactory Capability scale (SOC, 1 item), the Self-Reported capability of Perceiving specific odors scale (SRP, 5 items), and the Olfactory-Related Quality of life scale (ORQ, 6 items) [20]. For every patient analyzed, mean values of each of the three scales were calculated. Then, the one-way repeated measures ANOVA was used to detect any statistically significant ($p < 0.05$) pre-post outcome change.

3. Results

The most relevant results are described in Table 2 and Figs. 1–3. For any of the outcomes assessed, a significant change-from-baseline improvement was reported, even though mean value ameliorations were more pronounced for olfactory function per se (SOC: from 3.6 to 5.6 out of 10; SRP: from 1.8 to 3.0 out of 5), rather than for health-related quality of life (ORQ: from 2.9 to 3.9 out of 6).

4. Discussion

Our clinical findings suggest that olfactory training can help patients with post-viral smell dysfunction. Even though this condition tends to gradually improve with time, observational evidence indicates that around 7 months after the onset of COVID-19-related long-lasting smell problems, over one fourth of the subjects reported no changes or were even getting worse [21]. In contrast with these findings, all patients

Table 2
Baseline and follow-up average measures of the ASOF scales.

	SOC		SRP		ORQ	
	T0	T1	T0	T1	T0	T1
Mean	3.6	5.6	1.8	3.0	2.9	3.9
[95%	[2.5;	[4.5;	[1.3;	[2.4;	[2.3;	[3.2;
CI]	4.7]	6.7]	2.4]	3.5]	3.6]	4.6]
ANOVA	p=0.016		p=0.008		p=0.044	

Table legends.
95% CI: 95% Confidence Interval.
SOC=Subjective Olfactory Capability scale.
SRP=Self-Reported capability of Perceiving specific odors scale.
ORQ=Olfactory-Related Quality of life scale.
T0=At baseline.
T1=At the end of the 30-day olfactory training protocol.

treated with our olfactory training protocol experienced a significant improvement in their smell function. Future trials with larger study samples should put this preliminary evidence to a test.

From a mechanistic point of view, olfactory loss is usually associated with a significant reduction in olfactory bulb volume and function [22], a disarray of the olfactory neuroepithelium and a reduction in the number of olfactory receptors [23,24]. However, the olfactory system can show unique regenerative capacities [25]. The beneficial effects of essential oils as olfactory cues are probably due to their saliency and the binding capacity of volatile molecules to olfactory and non-olfactory receptors of the nasal mucosa: these mechanisms may favor regenerative processes, with promising preclinical [26,27] and clinical results [28,29,30,31,32,33,34,35,36].

In fact, it appears that olfactory training leads to significant changes both at a peripheral and at a central level. The peripheral, bottom-up mechanisms seem to involve the olfactory neuroepithelium, with an increased olfactory expression and signs of cell stimulation (migrating neuroblasts, neural precursor cells, olfactory ensheathing cells) [36,27], *via* an initial stimulation of olfactory receptors followed by neurogenesis or enhanced synaptogenesis [37,38]. Odor stimulation can increase electro-olfactogram responses, and revert loss of olfactory receptor activity and improve atrophy of the olfactory bulb [39,40].

The central, top-down, mechanisms regulate improvement in olfactory and verbal functions (odor detection threshold, odor discrimination and identification) [33,34,41,42], cortical changes [28,34], modifications in brain connectivity [43] and increase in olfactory bulb volume [44]. In fact, olfactory training may induce extensive re-organizational processes in brain areas other than the olfactory one, and may strengthen higher cognitive function [40]. There appear to be psychological effects *via* the direct neural connections between the amygdala–hippocampal complex and the olfactory neuroepithelium [34,43].

Apart from the evidence that olfactory training can trigger central and peripheral changes, there is a dearth of data relative to the exact mechanisms of action of odorant molecules. In fact, since it has been demonstrated that even a low concentration of odorants can influence the patients' recovery rate, it has been suggested that even the act of sniffing alone might have a positive effect on the outcome [33,34]. However, other scientists have only found marginal effects from the act of sniffing, thus highlighting the importance of specific volatile compounds inhaled by the study participants [29]. In the available trials published so far, the specific identity of olfactory stimuli was not deemed important, and in fact many of the olfactory stimuli used in the various tests were not real essential oils but synthetic reconstructions, or isolated molecules, and there never was the intent to analyze whether some stimuli were more effective than others, probably because the specific identity of the stimuli was not considered as important as the ease of recognition of the stimuli and the consequent stimulation of olfactory memory [45]. Researchers have selected the odorants among panels of different smells, with the intent to stimulate a large number of receptors and wide brain regions. To do this, scientists have mostly used
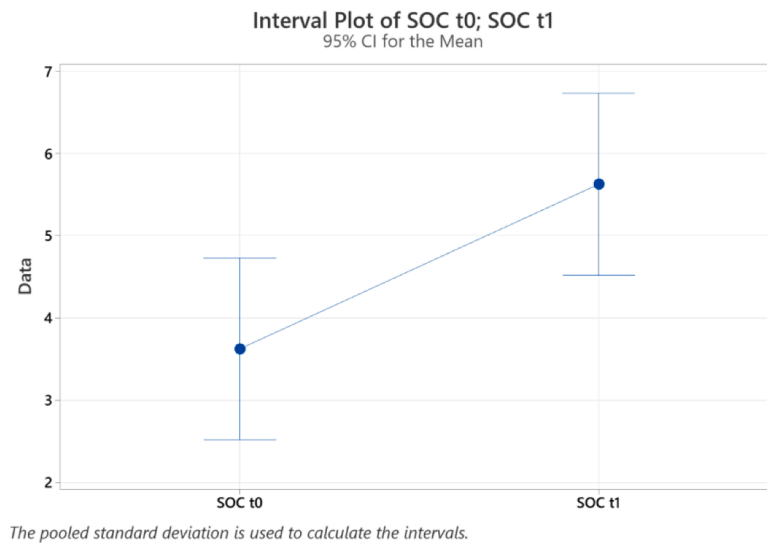
Fig. 1. Pre-post changes in the SOC scale values.
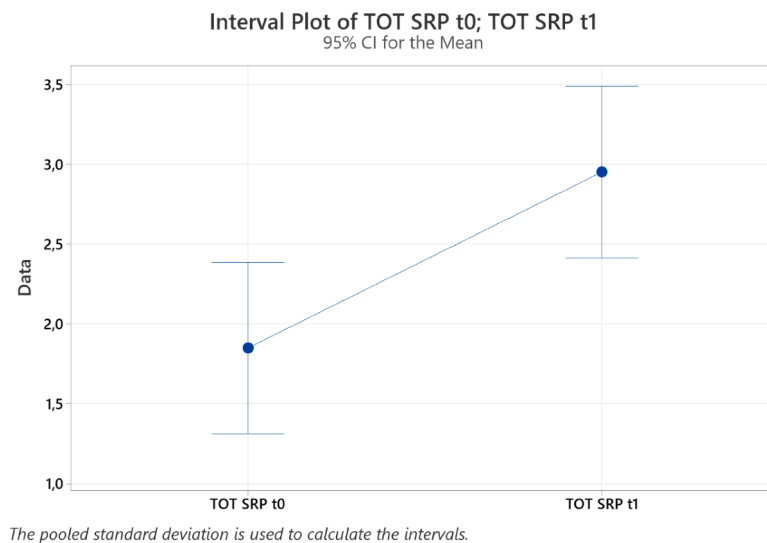
Fig. 2. Pre-post changes in the SRP scale values.

classical perfumery classifications, which have the limit of being quite subjective and often overlapping.

In this study, the choice of odorants has followed the same logic, but different classifications have been used (for example, the Gamble and Henning's [13] and Roudnitska's [10] classifications). Rather than only selecting one essential oil for each element of Henning's odor prism [13], it has been decided to include a larger set of essential oils because it was observed that this option is associated with higher rates of clinical improvements in patients with postinfectious olfactory loss [46]. Additionally, when possible, the authors have considered the chemical structure of dominant molecules included in each essential oil, following the hypothesis that chemosensory perception is influenced by the molecular structure of volatile compounds. Moreover, essential oils were also chosen for their content in molecules capable of binding to non-olfactory receptors, such as the members of the transient receptor potential (TRP) family of cation channels. TRP channel activation results in a sensory modality called "trigeminality" or "chemesthesis", which is related to the perception of texture, temperature, and pungency [47], but it might also play important functional roles in mammalian olfaction [48]. In this regard, current mechanistic data suggest a potential role of TRP channels in neurogenic and olfactory neuroepithelium

inflammation in COVID-19 [49]. Finally, it has been proposed that the effects of the essential oils used in olfactory training depend on anti-inflammatory effects of some of their constituents, such as eugenol, 1,8.cineole, geraniol and limonene [50]. Nevertheless, the concentration of these molecules in the olfactory neuroepithelium during olfactory training is unlikely to be sufficient to cause significant effects, and this mechanism would not explain the top-down effects observed after the rehabilitation protocol.

The set of essential oils used in this study represents a fairly wide range of odors with few overlaps. Additionally, the essential oils are almost all easily identifiable, and have also been selected for the presence of biomolecules active on TRP receptors, hoping that, in cases of very strong anosmia, this further stimulation, not linked to the olfactory epithelium, can facilitate the connection with odor memories.

4.1. Patient perspectives

All patients reported that the treatment proposed was well tolerated. Some of them declared that, at first, the olfactory training protocol was not so easy to memorize and, in order to avoid mistakes, the patients were given a full list of written instructions with references to the
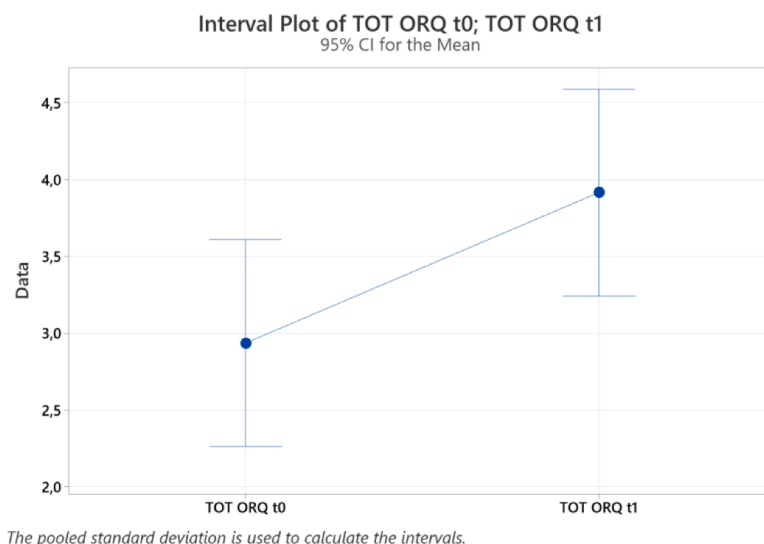
Fig. 3. Pre-post changes in the ORQ scale values.

essential oils and their order of inhalation. After almost losing their hope to recover their smell dysfunction, the patients were also happy to work on their health condition, for which very limited treatment options actually exist.

4.2. Study limitations

This report only involved a limited number of patients with heterogeneous comorbidities, and there was no control group to compare the efficacy of the intervention. The follow-up period coincided with the treatment duration, and there were no additional check-ups scheduled. Sources of bias typical of observational reports [51] and potentially associated with an overestimation of the treatment efficacy, such as selection bias, cannot be excluded. For this reason, large controlled studies are needed to test the efficacy of the intervention in subjects with smell dysfunction. All health-related information of the patients described were reported in Table 1 in order to minimize the so-called "information bias" and account for potential confounding factors. Finally, only a specific set of plant-derived essential oils was used, but other combinations may be possible and should be compared with each other.

5. Conclusion

In conclusion, it was observed that patients with long-lasting COVID-19-related smell dysfunction improved after a 30-day olfactory training protocol. Beneficial effects were described in terms of subjective olfactory capability, self-reported capability of perceiving specific odors and olfactory-related quality of life. In the future, clinical studies, possibly including a placebo control group and a large study population, would be useful to better investigate and test the role of olfactory training in patients with post-viral smell dysfunction.

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CRediT authorship contribution statement

Davide Donelli: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing original draft, Writing review & editing, Visualization,

Supervision, Project administration. **Michele Antonelli:** Methodology, Software, Validation, Formal analysis, Data curation, Writing original draft, Writing review & editing, Visualization. **Marco Valussi:** Methodology, Validation, Resources, Writing original draft, Writing review & editing, Visualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M.V. is a partner in the company Magnifica Essenza srl (Cavalese (TN), Italy) an essential oil manufacturing company. The other authors (D.D. and M.A.) have no competing interests to declare.

Data availability

Not applicable.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eujim.2023.102253.

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